REMARKS

Claims 17-23 are pending in the present application. The claims currently stand rejected under 35 U.S.C. §103 as discussed below. Claims 1-16 and 24 have been canceled without prejudice or disclaimer and pursuant to the Restriction Requirement. Reconsideration is respectfully requested.

Rejection Under 35 U.S.C. §103

Claims 17-23 remain rejected under 35 U.S.C. §103(a) as being unpatentable over Williamson *et al.* (Williamson, R., Curator, Deafness Gene Mutation Database, URL: http://hearing.harvard.edu/db/genelist.htm, last updated September 18, 2002) in view of Guo *et al.* (Guo *et al.* 2002. *Genome Res.* 12:447-457). The Examiner alleged that it would have been *prima facie* obvious to one of ordinary skill in the art to detect SNPs relevant to a human hearing loss associated with genes and mutations taught by Williamson by adapting the simultaneous detection of such SNPs in an exon specific array format as taught by Guo. Applicants respectfully traverse the rejection.

The present application claims priority to U.S. Application No. 10/373,978, filed on February 24, 2003 (*see*, paragraph [0001] of the specification). Williamson *et al.* is a website which discloses a generic list of mutations in genes related to hearing loss. According to the Williamson website, the status of the genes listed was "last updated" on September 18, 2002. However, the fact that the status of the listed genes is shown as "last updated" on September 18, 2002 does not mean that this information was publicly available as of this date. An internet archive tool, the "waybackmachine," available at http://www.archive.org/web.php, indicates that the Williamson website was publicly available from May 10, 2003. No data is available on the existence of the Williamson website for the time period prior to May 10, 2003. Therefore, it appears that Williamson *et al.* was not available to the public prior to May 10, 2003. As such Williamson *et al.* does not constitute prior art to the present application.

Notwithstanding the above, even if Williamson *et al.* constituted prior art, the references do not provide any reason to make the cited combination, nor do the references provide a reasonable expectation of success in such a combination. As a result, the Examiner has not made a *prima facie* case of obviousness. However, even assuming *arguendo* that the Examiner has established a *prima facie* case of obviousness, secondary factors, including unexpected results

and long felt need, strongly weigh against a finding of obviousness. Applicants submit herewith a factual declaration of John H. Greinwald, Jr., M.D., FAAP ("Greinwald Declaration"), with accompanying citations, as proper under 37 C.F.R. § 1.132, asserting, *inter alia*, that (1) the claimed microarrays are unexpectedly advantageous for the diagnosis of hearing loss and (2) such microarrays also satisfy the long-felt need for accurate, simple, efficient and highly cost-efficient diagnosis of hearing loss which may or may not be unrelated to mutation in the GJB2 gene.

Secondary factors

Secondary considerations must be considered in every case where they are presented. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983); *KSR International Co. v. Teleflex Inc.*, 550 U.S. ____ (2007). These include factors such as unexpected results, long-felt need, and failure of others. *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1380 (Fed. Cir. 1986); *Graham v. John Deere*, 383 U.S. 1 (1966).

Unexpected Results

Unexpected results can rebut a *prima facie* case of obviousness because that which would have been surprising to a person of ordinary skill in a particular art would not have been obvious. *In re Soni*, 54 F.3d 746 (Fed. Cir. 1995). The principle applies most often to the less predictable fields, as in the present case, where minor changes in a product or process may yield substantially different results. *Id.*

As will be discussed further below, Applicants disagree that the Examiner has established a *prima facie* case of obviousness. However, even assuming *arguendo* that a *prima facie* case of obviousness has been established, Applicants submit that the unexpected results of the claimed microarrays necessitate a finding of nonobviousness.

In Applicants' experiments, it has been unexpectedly found that pathogenic biallelic mutations were only found in MYO7A, OTOF, PDS (also known as SLC26A4) and CDH23 in pediatric patients with sensorineural hearing loss (SNHL) screened for mutations in a panel of thirteen known hearing loss associated genes (Greinwald Declaration, ¶¶9-10). Prior to the filing date of the present application, other than the GJB2 gene, the key components in SNHL in children were unknown. In addition, Applicants' compilation and analysis of hearing loss genes

based on the prevalence of mutations in population and family studies, and the impact of the gene toward communication, resulted in the surprising finding that mutations in the CDH23, MYO7A, OTOF, SLC26A4 and USH2A genes are more prevalent in hearing loss patients than mutations in other genes (Greinwald Declaration, ¶8). Therefore, a microarray comprising genetic sequences from CDH23, MYO7A and OTOF, SLC26A4 and USH2A is unexpectedly better for diagnosis of hearing loss than an array comprising any five randomly chosen known hearing loss genes.

Long-Felt Need

Recognition of need, and difficulties encountered by those skilled in the field, are classical indicia of unobviousness. *In re Dow Chemical Co.*, 837 F.2d 469 (Fed. Cir. 1988). Approximately 1 in 700 children are affected by sensorineural hearing loss (SNHL) and genetic factors are present in about 50% of these cases (Morton *et al.* (1991) *Ann NY Acad Sci*, 630:16-31). Despite the identification of 41 genes for nonsyndromic hearing loss, only a few clinical tests have been developed, largely due to the high cost of standard sequencing techniques (Hacia, J. G. (1999) *Nat Genet*, 21:42-47). The current medical evaluation of hearing loss involves a combination of laboratory and radiographic tests, few of which provide diagnostic or prognostic information (Greinwald Declaration, ¶7). These tests are costly, time-consuming, and stressful for the child and family (Greinwald Declaration, ¶7). Most recently, genetic testing of the GJB2 gene has been added to the diagnostic evaluation (Greinwald Declaration, ¶7). Mutations in this gene account for about 20% of children with sensorineural hearing loss (SNHL) with nonsyndromic congenital hearing loss. Greinwald *et al.*, *Arch Otolaryngol Head Neck Surg,* 128:84-7) (Greinwald Declaration, ¶7). However, beyond the GJB2, it was uncertain what genetic mutations are next most prevalent in patients with hearing loss (Greinwald Declaration, ¶7).

As discussed above, Applicants' compilation and analysis of hearing loss genes based on the prevalence of mutations in population and family studies, and the impact of the gene toward communication, resulted in the surprising finding that mutations in the CDH23, MYO7A, OTOF, SLC26A4 and USH2A genes are more prevalent in hearing loss patients than mutations in other genes (Greinwald Declaration, ¶8). The claimed microarrays would be a more comprehensive

diagnostic evaluation and provide a better understanding of the genotype-phenotype correlations, which could direct specific therapeutic interventions for hearing loss. Thus, the claimed microarrays fulfill the need for a tool for the accurate, simple, efficient and highly cost-efficient diagnosis of hearing loss.

In summary, Applicants submit the evidence of record and presented herein including unexpected results and long-felt need is strong evidence of the nonobviousness of the claimed microarrays. According to Dr. Greinwald, the procedures used for hearing loss diagnosis to date provide little or no diagnostic or prognostic information (Greinwald Declaration, ¶8). Beyond GJB2, it was uncertain what genetic mutations are next most prevalent in patients with hearing loss (Greinwald Declaration, ¶7). Also, key genes commonly found mutated in SNHL, aside from GJB2, were previously unidentified. (Greinwald Declaration, ¶¶9-10). Microarrays comprising genetic sequences from CDH23, MYO7A and OTOF, SLC26A4 and USH2A satisfy the long-felt need for a tool for the accurate, simple, efficient and highly cost-efficient diagnosis of hearing loss. (Greinwald Declaration, para. 11). In addition, such microarrays satisfy a need for tools for providing diagnostic and/or prognostic information on hearing loss. Applicants submit that even if the Examiner maintains that a *prima facie* case of obviousness has been established, these secondary considerations necessitate a finding of nonobviousness.

Lack of Reason for the Combination

In the Court's recent decision in *KSR International Co. v. Teleflex Inc.*, 550 U.S. _____ (2007), the Court repeatedly emphasized the value of determining if there is any "reason to combine" the various teachings in the art. The Court noted that "[a] patent composed of several elements is not proved obvious merely by demonstrating that each element was, independently, known in the prior art." (*KSR*, Syllabus, page 4 and page 14).[1] Thus, the Court has made it abundantly clear that some reason to combine the various elements must be present in order to establish a *prima facie* case of obviousness.

[1] The Court also noted that "it can be important to identify a reason that would have prompted a person of ordinary skill in the art to combine the elements as the new invention does." (KSR, Syllabus, page 5; see also, page 15). Additionally, the Court noted that "inventions in most, if not

Without the benefit of Applicants' disclosure, there would be no reason for one of skill in the art to combine the teachings relating hearing loss gene mutations in Williamson with the unrelated teachings of a microarray directed for high-throughput SNPs analysis of MHC Class I genes in Guo.

Williamson teaches a generic list of mutations in genes related to hearing loss. In stark contrast to Applicants' findings, the list of hearing loss mutations in Williamson *et al.* provides no prioritization to the importance or prevalence of these mutations or genes in a population (Greinwald Declaration, ¶11).

Guo is focused upon identification of SNPs related to MHC Class I genes for genetic variation analysis and population/epidemiology studies. There is no teaching or suggestion in Guo to define a disease phenotype based on these benign polymorphisms. Guo is silent as to any hearing loss gene, mutation or SNP (Greinwald Declaration, ¶12).

Therefore, the Examiner has not provided clear and particular evidence that there is a reason to combine Williamson with Guo for a **diagnostic** hearing loss microarray or kit comprising the sequences as claimed.

Furthermore, even if there were some suggestion to combine the isolated disclosures, there would not be any reasonable expectation of success produced by the combination. The list of hearing loss mutations in Williamson provides no prioritization to the importance or prevalence of these mutations or genes in a population (Greinwald Declaration, ¶11). One of ordinary skill in the art would not know, based on the generic list of genes provided in Williamson, to pick the specific genetic sequences as claimed. Guo is silent as to any hearing loss gene, mutation or SNP. The combination of Williamson and Guo would require an undue amount of experimentation to select genes that would render a microarray or kit effective as a diagnostic hearing loss device. Therefore, one of skill in the art would not expect any degree of success for a diagnostic hearing loss microarray as claimed, based on the scant information provided by the combination of cited references.

In summary, Applicants submit that there is no reason to combine the references, and one of ordinary skill in the art would have no reasonable expectation of success; therefore, no *prima*

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all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." (*KSR*, page 15).

facie case of obviousness has been established. Thus, Applicants respectfully request that the rejections be withdrawn.

Conclusion

Applicants have endeavored to address all of the Examiner's concerns as expressed in the outstanding Office Action. Accordingly, arguments in support of the patentability of the pending claim set are presented above. In view of the foregoing remarks, Applicants respectfully submit that this application is in condition for allowance and request the same. If any issues remain, the Examiner is cordially invited to contact the undersigned in order to resolve such issues promptly.

No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, the Applicants are not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. The Applicants reserve the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that the Applicants have made any disclaimers or disavowals of any subject matter supported by the present application.

Related Applications of Assignee

Applicant wishes to draw to the Examiner's attention to the following related applications of the present application's assignee.

Serial Number	Title	Filed
10/373978	MICROARRAY-BASED DIAGNOSIS OF PEDIATRIC HEARING IMPAIRMENT-CONSTRUCTION OF A DEAFNESS GENE CHIP	02/24/03

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 12-7-2007

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